REMARKS

Reconsideration and withdrawal of the rejections of the application are respectfully requested in view of the amendments and remarks herein.

I. STATUS OF THE CLAIMS AND FORMAL MATTERS

Claims 40-51 are now pending. New claims 48-51 have been added, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents.

No new matter is added.

It is submitted that these claims are in full compliance with the requirements of 35 U.S.C. §112. The amendments to the claims and the remarks herein are not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112; but rather the amendments and remarks are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Support for the new claims is found throughout the specification and the claims as originally filed.

II. THE OBJECTION TO THE CLAIMS IS OVERCOME

Claim 43 was again objected to as being dependent upon a rejected base claim. Applicants respectfully submit that the remarks and enclosures herein have overcome the rejections of claim 40, upon which claim 43 depends. Accordingly, it is respectfully believed that claim 43 is now allowable, and reconsideration and withdrawal of the objection to the claim is respectfully requested.

III. THE WRITTEN DESCRIPTION REJECTION IS OVERCOME

Claims40 and 44 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The rejection is respectfully traversed.

The Office Action indicates that "the specification fails to provide adequate written description for the genus of disorders of keratinization" and states that it is unclear whether "Applicant has provided Darriers disease as the sole exemplary disorder of keratinization or

whether Applicant has provided Darriers disease, palmoplantar keratoderma, etc. as exemplary disorders of keratinization". Office Action at 4.

Applicants respectfully submit that the specification provides numerous examples of disorders of keratinization, including Darriers disease, hyperkeratoses, palmoplantar keratoderma, the icthyosis (which includes non-bullous ichthyosiform erythroderma), pityriasis rubra pilaris, erythrokeratoderma variabilis, lichen planus, epidermal naevoid syndromes (which can be associated with Darriers disease) and cutaneous lupus erythematosus. One of skill in the art, reading the specification at page 51, lines 15-20 would, without any difficulty, readily understand which of the listed disorders were examples of disorders of keratinization.

Indeed, Applicant also reminds the Examiner that "[t]he specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public". *See*, e.g., MPEP § 2164.05(a), *In re Buchner*, 929 F.2d660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984).

Thus, to the extent that the Office believes the listing of disorders to be unclear, Applicants respectfully direct the Examiner's attention to Exhibit 1, which provides abstracts of (1) Milstone et al. "Serum parathyroid hormone level is elevated in some patients with disorders of keratinization", Arc. Dermatol. 1992; 128(7):926-30; (2) Kragballe et al. "Efficacy, tolerability and safety of calcipotriol ointment in disorders of keratinization. Results of a randomizaed, double-blind, vehicle controlled, right/left comparative study", Arch. Dermatol. 1995; 131(5):556-60; and a full copy of Lavrijsen et al., "Barrier function parameters in various keratinizaiton disorders: transipidermal water loss and vascular response to hexyl nicotinate", British J. of Dermatol. 1993; 129:547-554.

Each of these references provides examples of disorders of keratinization, including those listed in the specification above. Thus, the state of the art clearly recognized those disorders encompassed by the term "disorders of keratinization", such that one of skill in the art reading the present application would fully appreciate the disorders listed that fall within disorders of keratinization. Thus, given the knowledge in the art at the time of filing, the listing provided in

the specification is more than sufficient to provide adequate written description for "disorders of keratinization".

Thus, reconsideration and withdrawal of the written description rejection is respectfully requested.

IV. THE INDEFINITENESS REJECTION IS OVERCOME

Claims 44-47 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. The rejection is respectfully traversed.

The Office Action stated that the claims were unclear as to whether the skin of the patient in need thereof is skin that is affected by the claimed hyperproliferative disease or if it is any skin on the subject who is in need of treatment. Applicants respectfully disagree and remind the Examiner that the claims are to be read in light of the specification.

The specification clearly indicates that the compositions of the invention can be applied "to that portion or area of the skin which is affected" or the areas "in which treatment is desired". Furthermore, the claimed application to skin would be fully understood by those of skill in the art as described above.

Accordingly, Applicants respectfully submit that the recitation of administration to skin of a patient in need thereof is sufficiently clear in view of the specification and the teachings of the art as a whole. Consequently, reconsideration and withdrawal of the indefiniteness rejection is respectfully requested.

V. THE ART REJECTIONS ARE OVERCOME

Claims 40-42 and 44-46 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Burchardt et al. (WO 97/15298).

The Office Action states that "Burchardt et al. teaches the treatment of acute and chronic inflammatory disorders, such as psoriasis . . . using a glucocorticoid steroid, such as carbenoxolone sodium . . . and an LTD4 receptor antagonist." Office Action at 8. The Office Action further notes that "Burchardt et al. expressly discloses that the combination can be used topically as an ointment or cream for application to the skin." Office Action at 8.

The Office Action further indicates that the use of the transitional phrase "consisting essentially of" does not limit "the scope of a claim to the specified materials or steps 'and those that doe not materially affect the basic and novel characteristic(s)' of the claimed invention" because Applicants "failed to definitely point out the basic and novel characteristics of the invention." Office Action at 8.

Applicants respectfully submit that the previously submitted arguments clearly identified the basic and novel characteristics of the present invention, namely the administration of an inhibitor of the retinoic acid biosynthetic pathway, wherein said inhibitor is carbenoxolone. As the use of carbenoxolone as **the** active ingredient is one of the basic and novel characteristics of the invention as described in the specification, Applicants respectfully submit that the phrase "consisting essentially of" would necessarily exclude a material change to the claimed administration of carbenoxolone, and that the use of an LTD4 receptor antagonist would be such a material change, and is therefore excluded from the claims.

Indeed, Applicants respectfully submit that the claims, as currently and previously pending, clearly indicated that the claimed method comprised the administration of **only a single inhibitor** of retinoic acid; thus, the inclusion of a second active would be a material change.

Indeed, as previously provided, this reading of the claims is clearly supported in the specification, in, for example, the Proliferation Assay discussed on pages 100 to 101 clearly indicates in Table 6 that carbenoxolone was administered in the presence of no other inhibitors (see line 6 of Table 6) and Figure 10 which provides the results obtained from the Proliferation Assay, with the carbenoxolone providing the greatest reduction in proliferation.

Furthermore, although the specification and claims clearly indicate that the presence of a second inhibitor would be a material change; Applicants again reiterate that the use of a single inhibitor of retinoic acid which is in direct contrast from Burkhardt which taught the use of the LTD4 receptor antagonist with optional use of glucocorticosteroids.

Applicants respectfully submit that this careful reading of Burkhardt is especially relevant in light of the fact that Burkhardt only mentions carbenoxolone sodium on page 2 in a list of 68 different examples of "customary" glucocorticosteroids. In contrast to the disclosure in Burkhardt, the attached Declaration of Professor Korting (Exhibit 2) makes it clear that carbenoxolone sodium and corticotrophin, which are included in the list of "customary glucocorticosteroids" found on page 2 of Burchardt, are in fact not glucocorticosteroids.

It is clear from Burkhardt that the authors are only interested in using combinations of a glucocorticosteroid with an LTD4 receptor antagonist in the treatment of inflammatory disorders. This is clear from, for example, the title and the first paragraph of Burkhardt. The authors of Burkhardt consider glucocorticosteroids to be important in inflammatory disorders, as noted in the second paragraph of this document.

Thus, a skilled person would not select the use of carbenoxolone sodium in combination with an LTD4 receptor antagonist. Not only is there no direct teaching of this combination, no suggestion of this combination, nor any motivation to try this combination, provided by Burkhardt, but also, a skilled person following Burkhardt would actually have a very good scientific reason to specifically avoid carbenoxolone sodium, namely the erroneous listing of carbenoxolone sodium as a glucocorticosteroid.

Indeed, as stated in Professor Korting's declaration, carbenoxolone sodium (and also corticotrophin), although being mentioned in the list of "customary glucocorticosteroids" on page 2 of Burkhardt, are not actually glucocorticosteroids. Sections 4 and 5 of Dr. Korting's declaration demonstrates that carbenoxolone sodium (and corticotrophin) are structurally quite distinct from glucocorticosteroids.

Furthermore, Section 3 of Professor Korting's declaration clearly indicates that not only would one of skill in the art would consider the inclusion of carbenoxolone sodium in the list of glucocorticosteroids appearing in Burkhardt to be a clear and obvious error, but that the skilled artisan would not sincerely consider using compounds which are not glucocorticosteroids in combination with LTD4 receptor antagonists for the purposes set out in Burkhardt.

Thus, since the skilled artisan would positively avoid the combination of carbenoxolone sodium with an LTD4 receptor antagonist, one of skill in the art would also positively avoid using the combination of carbenoxolone sodium with an LTD4 receptor antagonist for the treatment of any of the conditions mentioned in Burkhardt.

Therefore, not only would the inclusion of a second receptor antagonist in the presently claimed invention amount to a material change of the invention and should therefore be excluded from the claims having the transitional language of "consisting essentially of", but one of skill in the art would not make the selections from Burkhardt described in the Office Action especially as in so doing the skilled artisan would be failing to consider a clear, obvious error present in

Burkhardt's list of glucocorticoid steroids. Thus, the present invention is clearly non-obvious over Burkhardt, especially in view of Dr. Korting's declaration.

Consequently, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, an interview with the Examiner is respectfully requested, prior to issuance of any paper other than a Notice of Allowance; and, the Examiner is respectfully requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

For the reasons stated above, applicant respectfully requests a favorable reconsideration of the application, reconsideration and withdrawal of the rejections of and objections to the instant application, and prompt issuance of a Notice of Allowance.

Respectfully submitted,
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